SUMMARY LEAD REVIEW MEMO
Restylane? Injectable Gel
P020023

Product Description:
Restylane consists of non-animal, stabilized, hyaluronic acid (NASHA) at a concentration of 20 mg/ml, suspended in a physiological buffer pH 7. It is a clear, transparent, viscous and sterile gel, supplied in a disposable glass syringe. Each syringe contains 0.4 or 0.7 ml gel. The contents of the syringe are sterile. The syringe consists of a plunger stopper, finger grip and plunger rod. The syringe is packed in a blister together with a sterile 30 G needle.

Restylane acts by adding volume to the tissue, thereby restoring the skin contours to the desired level of correction.

Indication for Use: Restylane is intended for temporary correction of moderate to severe facial wrinkles and folds, such as nasolabial folds.

Marketing History
Restylane was first approved for marketing and sale in September 1996 in the European Union including EES. Registration was obtained in Canada, Brazil, Hungary and Russia in 1998. In 1999 the product was registered in Australia, Argentina, Peru, Poland and Korea. In 2000 Ecuador, Mexico, Uruguay, Turkey and Singapore were added to the list of countries in which Restylane is approved. Approval was obtained in Bulgaria, Columbia. Czech Republic, and Jordon in 2001.

Sales for 1997 amounted to 67,050 syringes and 457,385 syringes sold worldwide in 2001.

Restylane has not been marketed in the United States was the subject of a clinical trial in the U.S.

Clinical Studies:
Two clinical studies have been performed in order to evaluate the safety and efficacy of Restylane for the treatment of facial wrinkles and folds. The pivotal study is the primary evaluation of safety and effectiveness. The open-label extension is considered only for additional safety data. Only a very brief summary of the clinical studies is provided here. Please see the FDA clinical summary memo for complete summary information on the clinical study.

1. Pivotal Study: A Randomized, Evaluator-Blind, Multi-Center U.S. Study Comparing the Safety and Efficacy of Restylane and Zyplast for the Correction of Nasolabial Folds

Study Design: Randomized, double-blind, multi-center clinical study on Restylane vs. Zyplast. A total of 138 patients at 6 centers were randomized to obtain the optimal cosmetic result. The response of the

initial treatment was evaluated after 2 weeks and in case of non-optimal cosmetic results a touch-up treatment could be performed. This procedure was repeated every two weeks until optimal response was achieved.

2. An open tolerance and efficacy study- A Non-Randomized Open Study of 112 Patients Receiving Restylane for the Treatment of Depressed Cutaneous Scars, Wrinkles and Folds

This study was done at four clinics with 112 patients treated and followed for four months. The naso-labial folds were the most commonly treated site but the study also included treatment of facial wrinkles, scars and lips.

The original submission contained the results of the pivotal clinical study out to 6 months and an open-label extension to the study. The pivotal study is considered by FDA to be the primary study of safety and effectiveness. The open-label extension is considered only for additional safety data. For ease of review, it is helpful to understand the chronology of the submission. FDA determined that the 6-month follow-up data were inadequate to make a judgment on the safety of the product and requested that the sponsor provide 12 month data that were being collected. Additionally, we requested that the sponsor provide all safety data from all sources, including those from Europe and patient diaries. Based on the data in the original submission, FDA sent the sponsor a major deficiency letter on November 18, 2002 requesting information addressing overall safety data and data regarding hypersensitivity. The sponsor submitted an amendment (i.e., Amendment 3) in response to the major deficiency letter of November 18, 2002. The sponsor was sent another major deficiency letter on May 5, 2003, to address the issues of biocompatibility/toxicology of the cross-linker component, hypersensitivity, and lack of minority representation in the study. In response to that letter, the sponsor submitted another amendment (i.e., Amendment 5). These letters and the sponsor's responses to the deficiencies are included on the CD ROM in the panel pack.

FDA ISSUES/CONCERNS

Restylane contains small amounts of BDDE (1,4 butanediol diglycidulether), a potential sensitizer. Hypersensitivity was therefore a concern. The IDE protocol had specified that patients developing sensitivity reactions were to be skin tested. The sponsor pointed out that none of the investigators noted sensitivity reactions and therefore none of the patients were skin tested. FDA is concerned that some of the reactions noted during the study could be hypersensitivity reactions. The panel will be asked to comment on this issue.

In addition to questions about the overall effectiveness of Restylane, FDA questions whether or not the data show Restylane as superior to the control (Zyplast). The sponsor bases their superiority claim on the majority of individual patient successes achieving a one-point improvement over the control in the Wrinkle Severity Rating Scale (SRS) from baseline at 6 months. The alternative approach is to look at the entire cohort of Restylane versus Control and note that a full one-point improvement could not be

achieved in the aggregate case (D = 0.58). The panel will be asked to discuss if Restylane is superior to the Control.

In addition to questions about the overall safety of Restylane, FDA has concerns about the lack of minority representation in the study. Minorities, particularly those with darker skin, may have more severe reactions to injections than populations with lighter skin. Noting that the study only included two African-Americans and ten patients listed as "other", dark skin populations may have an increased risk of adverse reactions or poor cosmetic outcome. The panel will be asked to discuss if the sponsor should be required to conduct further studies on the issue and if Restylane should include language in the labeling to address the lack of minorities in the study.

FDA also questioned whether the data in the PMA supported the proposed indications. The sponsor had only injected nasolabial folds bilaterally (i.e., control and treatment sides) yet the proposed indications include "…correction of moderate to severe facial wrinkles and folds..." FDA will also ask the panel to comment on the adequacy of the data for these proposed indications.